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ANNUAL REVIEWS

Annual Review of Immunology

Host Control of Fungal Infections: Lessons from Basic Studies and Human Cohorts

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Annu. Rev. Immunol. 2018. 36:157–91

First published as a Review in Advance on December 13, 2017

The *Annual Review of Immunology* is online at immunol.annualreviews.org

https://doi.org/10.1146/annurev-immunol-042617-053318

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Keywords

fungi, antifungal immunity, monogenic disorders, acquired immunodeficiencies, fungal vaccines, immunotherapy

Abstract

In the last few decades, the AIDS pandemic and the significant advances in the medical management of individuals with neoplastic and inflammatory conditions have resulted in a dramatic increase in the population of immunosuppressed patients with opportunistic, life-threatening fungal infections. The parallel development of clinically relevant mouse models of fungal disease and the discovery and characterization of several inborn errors of immune-related genes that underlie inherited human susceptibility to opportunistic mycoses have significantly expanded our understanding of the innate and adaptive immune mechanisms that protect against ubiquitous fungal exposures. This review synthesizes immunological knowledge derived from basic mouse studies and from human cohorts and provides an overview of mammalian antifungal host defenses that show promise for informing therapeutic and vaccination strategies for vulnerable patients.

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INTRODUCTION

Despite an estimated 5,000,000 fungal species, fewer than 100 regularly infect humans. They cause superficial infections, primarily in immunocompetent individuals, and opportunistic, invasive, life-threatening infections, primarily in immunosuppressed patients. Fungi exhibit various morphologic states that facilitate virulence during infection. Spherical yeasts (*Cryptococcus*), molds with branching hyphae (*Aspergillus/Rhizopus*), interchanging yeasts and pseudohyphae (*Candida*), and endemic dimorphic fungi that assume mold morphology in the environment and yeast morphology in human tissues (*Histoplasma/Blastomyces/Paracoccidioides*) are most common. The global fungal disease burden is substantial—invasive infections collectively cause hundreds of thousands of deaths worldwide each year (1). Although not life-threatening, superficial fungal infections are common; for example, ~75% of women develop vulvovaginal candidiasis and ~10% of all humans develop onychomycosis.

In recent decades, the introduction of myeloablative chemotherapy for malignancies, of glucocorticoids and other immunomodulators for autoimmunity, and of transplantation for end-organ failure has, alongside the AIDS pandemic, contributed significantly to the emergence of opportunistic mycoses. Moreover, novel pathogenic (including multidrug-resistant) fungi have emerged to pose new threats to humans (*Candida auris/Cryptococcus gattii*), bats (*Pseudogymnoascus destructans*), and amphibians (*Batrachochytrium dendrobatidis*) (2). Therefore, interest in fungal immunology research has recently intensified to instruct treatment and vaccine strategies for fungus-infected individuals. Herein, we summarize our understanding of the cellular and molecular basis of antifungal immunity, focusing on evidence from clinically relevant mouse models of mycoses and patient cohorts with inherited and acquired fungal infection susceptibility. Immune responses in allergen- or toxin-mediated fungal diseases and immune regulation driven by endogenous mycobiota are reviewed elsewhere (3–5).

INNATE IMMUNITY AGAINST FUNGI: FROM RECOGNITION TO ELIMINATION

Despite continuous environmental exposure to ubiquitous fungi via the lungs, gut, and skin, the overwhelming majority of these encounters do not cause human disease. This is largely achieved by innate immune mechanisms that effectively sense and eliminate fungi.

Fungal Recognition

Innate fungal recognition is accomplished via sensing of cell wall and intracellular pathogen-associated molecular patterns (PAMPs) by soluble, membrane-bound, and intracellular pattern recognition receptors (PRRs) of myeloid and epithelial cells (**Table 1**). Fungal recognition promotes cytokine and chemokine production; enables reactive oxygen species (ROS) production, fungal uptake, and killing by phagocytes; and modulates the development of adaptive T cell responses (described below). The cell wall of eukaryotic fungi is positioned outside the plasma membrane and predominantly comprises rigid polysaccharide layers. Although cell wall composition varies between fungal species and between morphogenic states of the same fungus, it is typically an inner chitin layer, an adjacent layer of β-(1, 3)- and β-(1, 6)-glucans, and an outer layer of N- and O-linked mannoproteins (*Candida*) or galactosaminogalactan and galactomannan (*Aspergillus*) (6). Fungi employ evasion strategies to avoid recognition, primarily by concealing PAMPs. For example, the galactoxylomannan and glucuronoxylomannan-containing *Cryptococcus* capsule, a major virulence factor, prevents fungal uptake by host cells. Moreover, masking

of immunoreactive β-glucan is achieved by a hydrophobin layer (*Aspergillus*), an α-glucan layer (*Histoplasma*/*Paracoccidioides*), or filamentation (*Candida*) (6, 7).

Fungal-recognizing PRRs include C-type lectin receptors (CLRs), Toll-like receptors (TLRs), complement, and others outlined in **Table 1** [reviewed in detail elsewhere (6–8)]. Fungal-specific inflammasome activation occurs via caspase-1, caspase-8, and caspase-11 pathways (9, 10).

Table 1 Fungal pattern recognition receptors and associated fungal pathogen–associated molecular patterns

PRR	Fungal PAMP	Fungal genera
Dectin-1 (CLEC7a)	β-Glucan	*Candida*, *Aspergillus*, *Cryptococcus*, *Histoplasma*, *Paracoccidioides*, *Pneumocystis*, *Exserohilum*
Dectin-2 (CLEC6a)	α-Mannans, *O*-linked mannoproteins	*Candida* (including *C. glabrata*), *Aspergillus*, *Coccidioides*, *Blastomyces*
Dectin-3 (CLEC4d)	α-Mannans	*Candida*
Mincle (CLEC4e)	α-Mannose, glyceroglycolipids	*Candida*, *Pneumocystis*, *Malassezia*, *Fonsecaea*
FcγR	Mannan, glucuronoxylomannan	*Candida*, *Cryptococcus*
CD23 (FcεRII)	α-Mannans, β-glucans	*Candida*
Mannose receptor (CD206)	Mannans, *N*-linked mannans, *N*-acetyl-D-glucosamine, glycoprotein A, chitin (?)	*Candida*, *Pneumocystis*
DC-SIGN (CD209)	Mannans, galactomannan	*Candida*, *Aspergillus*
CR3 (CD11b/CD18)	β-Glucan, mannan, glucuronoxylomannan, HSP60, BAD-1	*Candida*, *Aspergillus*, *Histoplasma*
TLR1	Glucuronoxylomannans (with TLR2)	*Cryptococcus*
TLR2	α-Glucans, mannan, glucuronoxylomannan, phospholipomannan	*Candida*, *Cryptococcus*
TLR4	*O*-linked mannans, rhamnomannans, glucuronoxylomannan	*Candida*, *Cryptococcus*, *Scedosporium*
TLR6	Glucuronoxylomannans, phospholipomannans (with TLR2)	*Candida*
TLR7	Fungal RNA	*Candida*
TLR9	Fungal DNA, chitin (?)	*Candida*, *Aspergillus*
NOD1	Unknown	*Aspergillus*
NOD2	Chitin (?)	*Candida*
NLRP3	Unknown	*Candida*, *Aspergillus*
NLRP10	Unknown	*Candida*
NLRC4	Unknown	*Candida*
MDA5	Unknown	*Candida*
CD36	β-Glucan	*Candida*, *Cryptococcus*
CD14	Mannan, glucuronoxylomannan	*Cryptococcus*, *Scedosporium*
Lactosylceramine	Unknown	*Pneumocystis*
Galectin-3	β-Mannosides	*Candida*
Pentraxin-3 (PTX3)	Galactomannan	*Aspergillus*
Surfactant proteins A and D	Mannan, β-glucan, glycoprotein A	*Candida*, *Aspergillus*, *Cryptococcus*

Abbreviations: CR3, complement receptor 3; DC-SIGN, dendritic cell-specific intercellular adhesion molecule-3-grabbing nonintegrin; MDA5, melanoma differentiation-associated protein 5; NLRC, NLR family CARD domain-containing protein; NLRP, NACHT, LRR, and PYD domains-containing protein 3; NOD, nucleotide-binding oligomerization domain; PAMP, pathogen-associated molecular pattern; PRR, pattern recognition receptor; TLR, Toll-like receptor.

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Activation of AIM2 and NLRP3, NLRP3 and NLRP10, and NLRC4 is protective during aspergillosis, invasive candidiasis, and mucosal candidiasis, respectively (10–12). Most PRRs recognize shared fungal PAMPs, but preferential PRR recognition also occurs, as with the CLR Mincle (CLEC4E) and mannosyl–fatty acids of *Malassezia*, the agent of dandruff (13). Importantly, the same PAMP may be recognized by cell-specific and fungus morphotype–specific PRRs. For example, mannan is differentially recognized on *Candida* yeasts versus hyphae by macrophage and dendritic cell (DC) mannose receptor (CD206), Dectin-2 (CLEC6A), and DC-SIGN (CD209). Similarly, β-glucan is predominantly recognized by Dectin-1 (CLEC7A) on mononuclear phagocytes and complement receptor 3 (CR3) on neutrophils (7). Furthermore, mice lacking individual PRRs exhibit variable strain-specific susceptibility to *Candida* and *Aspergillus*, reflecting differential strain-specific dependence on individual TLRs and CLRs during infection (14). Future studies using conditional knockout mice should define the relative contribution of individual PRRs on different myeloid cells and the integration of cell-specific and fungus-specific PRR recognition in vivo. To add complexity, synergistic PRR interactions occur, which broaden PAMP sensing and enhance or restrain immune responses. For example, CLR-dependent recognition of *Fonsecaea pedrosoi*, agent of the tropical chronic skin infection chromoblastomycosis, is insufficient to control infection but is reinstated by TLR costimulation. Notably, topical application of the TLR7-agonist imiquimod is successful in some patients with chromoblastomycosis (15, 16).

Because Mendelian disorders in CLR signaling, not other fungus-recognizing PRRs, cause fungal susceptibility (described below), we focus on CLR signaling (**Figure 1**), primarily downstream of Dectin-1. Binding of Dectin-1 by β-glucan activates immune responses to numerous fungi (*Candida*, *Aspergillus*, *Histoplasma*, *Coccidioides*, *Paracoccidioides*, *Pneumocystis*). Dectin-1 engagement promotes Src-dependent phosphorylation of its immunoreceptor tyrosine-based activation motif (ITAM), recruits the SHP-2 tyrosine phosphatase and activates spleen tyrosine kinase (Syk) (17). In contrast, engagement of Dectin-2, Dectin-3 (CLEC4D), or Mincle requires partnering with the ITAM-containing adaptor FcRγ for Syk activation (6). Downstream of Syk, the Vav proteins and protein kinase C-δ phosphorylate CARD9 (caspase recruitment domain–containing protein 9), which partners with TRIM62, forms the CARD9/BCL-10/MALT1 complex, and activates the canonical NF-κB subunits p65 and c-Rel (18–20). Dectin-1 also couples H-Ras and Ras-GRF1 to promote CARD9-dependent ERK activation (21). In addition, Dectin-1-mediated RAF-1 phosphorylation activates the noncanonical NF-κB subunit RelB, and Dectin-2-mediated activation of phospholipase Cγ2 relays CARD9-independent signals to NK-κB, ERK, and JNK (22, 23). Consonant with the crucial role of CLR/Syk/CARD9 signaling in antifungal immunity, mice lacking Card9 or Syk are hypersusceptible to candidiasis, aspergillosis, and cryptococcosis (24, 25).

Conversely, CLR/Syk signaling may negatively regulate innate immunity. For example, Dectin-1-mediated JNK1 signaling downregulates the expression of the CLR CD23 (FcεRII), impairs CD23-dependent nitric oxide production, and decreases survival during systemic candidiasis (26). Moreover, the E3-ubiquitin ligase CBLB inhibits innate responses in macrophages and DCs by targeting Dectin-1, Dectin-2, and Syk for ubiquitination and degradation. Hence, CBLB impairs ROS production, fungal killing, inflammasome activation, and survival during systemic candidiasis (27). Therefore, CD23 and CBLB are potential therapeutic targets for systemic mycoses.

Professional Phagocytes: Recruitment and Effector Function

Professional phagocytic cells such as neutrophils, resident macrophages, monocytes, and monocyte-derived DCs are the first responders during fungal invasion. Recent studies have shed light on the molecular mechanisms that promote their recruitment and effector function during a variety of fungal infections.

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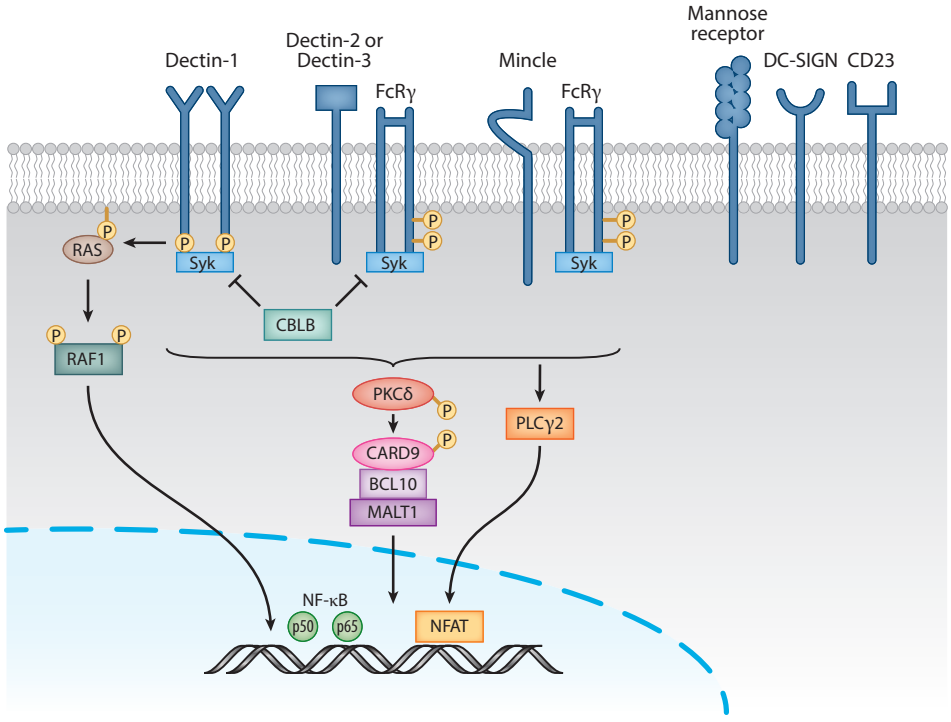

Figure 1

Fungal recognition by CLR signaling. CLRs such as Dectin-1 (CLEC7A), Dectin-2 (CLEC6A), Dectin-3 (CLEC4D), Mincle (CLEC4E), MR (CD206), and DC-SIGN (CD209) on the surface of myeloid cells sense fungal cell wall polysaccharides (detailed description in **Table 1**). Following Dectin-1 engagement, displacement of the phosphatases CD45 and CD148 around Dectin-1 promotes Src-dependent phosphorylation of the Dectin-1 ITAM, which results in activation of Syk. Engagement of Dectin-2, Dectin-3 (which forms heterodimers with Dectin-2), or Mincle requires partnering with the ITAM-containing adaptor FcRγ for Syk activation. The E3 ubiquitin ligase CBLB, which ubiquitinates Dectin-1, Dectin-2, and Syk, inhibits immune responses downstream of Dectin-1 and Dectin-2. Downstream of Syk, PKCδ phosphorylates CARD9 and promotes the assembly of the CARD9/BCL-10/MALT1 complex, which relays signals to the canonical NF-κB subunits p50 and p65 via the kinase TAK1. Dectin-1 also activates NF-κB via the noncanonical RAF-1 signaling cascade. Dectin-2-mediated activation of phospholipase Cγ2 promotes CARD9-independent activation of NF-κB, ERK, and JNK. CD23 (FcεRII) is a newly described CLR that is upregulated upon Dectin-1 engagement and leads to nitric oxide production. The signaling cascades downstream of CD23, MR, and DC-SIGN are poorly understood. Abbreviations: BCL-10, B cell lymphoma/leukemia 10; CARD9, caspase recruitment domain–containing protein 9; CBLB, casitas B-lineage lymphoma b; CLR, C-type lectin receptor; DC-SIGN, dendritic cell–specific ICAM3-grabbing nonintegrin; ERK, extracellular signal–regulated kinase; FcRγ, Fc receptor common γ chain; ITAM, immunoreceptor tyrosine-based activation motif; JNK, c-Jun N-terminal kinase; MALT1, mucosa-associated lymphoid tissue lymphoma translocation protein 1; MR, mannose receptor; NF-κB, nuclear factor-κB; NFAT, nuclear factor of activated T cells; PKCδ, protein kinase C-δ; PLCγ2, phospholipase Cγ2; Syk, spleen tyrosine kinase; TAK1, transforming growth factor β–activated kinase 1.

Neutrophils. Mouse neutrophils are critical for protection during invasive candidiasis, aspergillosis, and mucormycosis, and neutropenia is a well-established risk factor for these infections [but not cryptococcosis, histoplasmosis, or *Pneumocystis jirovecii* pneumonia (PJP)] in humans. Early neutrophil recruitment to the fungus-infected tissue is essential for pathogen clearance (28) (**Figure 2**). Indeed, delayed neutrophil accumulation in kidney versus liver or spleen correlates

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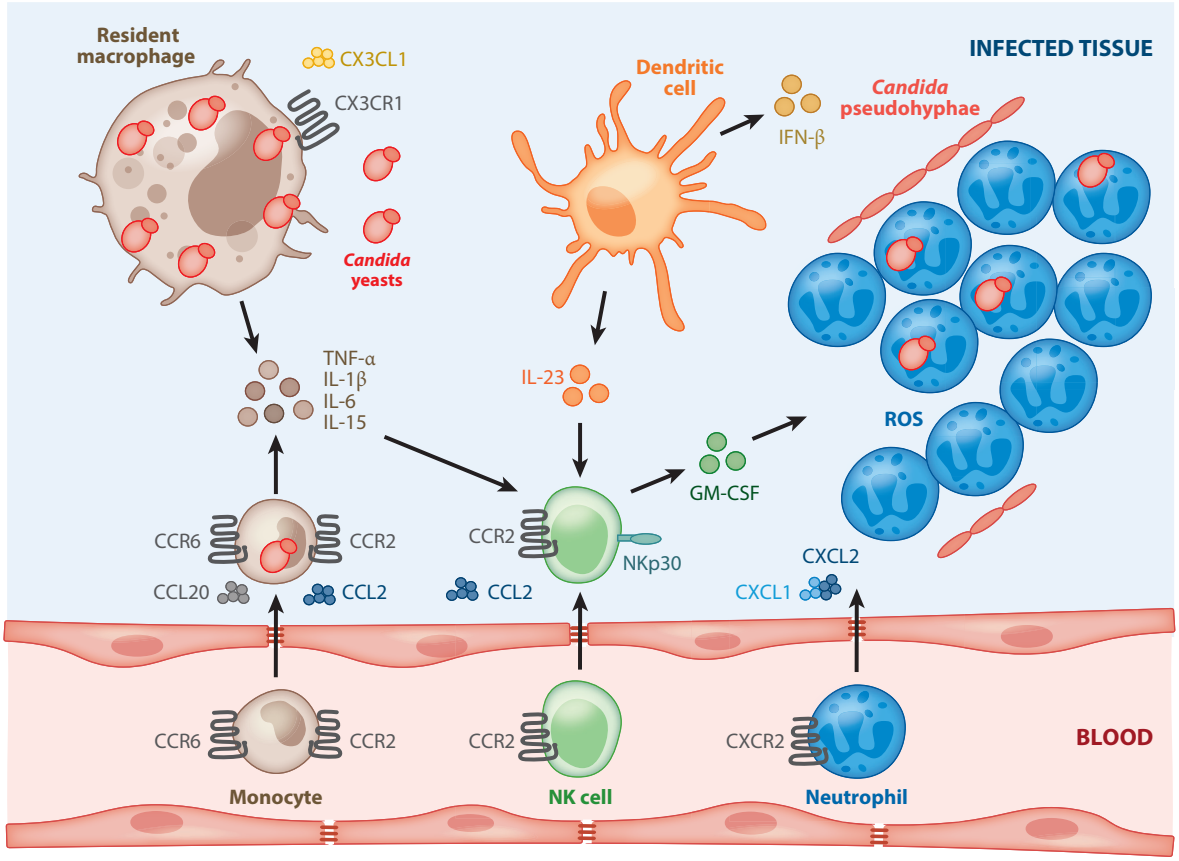

Figure 2

Recruitment and effector function of professional phagocytes during fungal invasion. Kidney-resident macrophages internalize invading *Candida* yeasts, ensnare *Candida* pseudohyphae, produce proinflammatory cytokines and chemokines, and exert direct fungal killing. The chemokine receptor CX3CR1 and its ligands CX3CL1 critically regulate resident macrophage survival, accumulation in tissue, and contact with *Candida* after fungal invasion. Inflammatory Ly6C^{hi} monocytes are recruited to the *Aspergillus*-, *Histoplasma*-, *Cryptococcus*-, and *Blastomyces*-infected lung and to the *Candida*-infected kidney and brain in a CCL2- and CCR2-dependent manner, whereas the CCL20-CCR6 chemokine axis promotes monocyte recruitment during neutropenic pulmonary aspergillosis. Monocytes produce proinflammatory cytokines and chemokines, directly kill fungi, prime neutrophil fungal killing, differentiate into inflammatory DCs, and orchestrate the development of adaptive immune responses. CD11b^{+} DCs produce type I interferons and secrete IL-23 in a Syk-dependent manner, which activates NK cells to produce GM-CSF, which primes the candidacidal activity of neutrophils. This NK cell–neutrophil cross talk is also mediated via IL-15 production by Ly6C^{hi} monocytes upon type I interferon activation. NK cells exert direct fungicidal activity via activation of their surface receptor NKp30. NK cell recruitment is mediated via CCL2-CCR2 during neutropenic pulmonary aspergillosis. Neutrophils are recruited to the *Aspergillus*-infected lung in a CXCL1/CXCL2-CXCR2-dependent manner and exert potent fungicidal activity via both oxidative and nonoxidative mechanisms. Abbreviations: DC, dendritic cell; GM-CSF, granulocyte macrophage colony-stimulating factor; NK, natural killer; ROS, reactive oxygen species.

with the kidney-specific inability to curtail *Candida* growth (29). IL-1α and CXCR2-targeted chemokines promote protective neutrophil trafficking into *Aspergillus*-infected lungs, whereas the corresponding signals during candidiasis remain unclear (30–32).

Following tissue recruitment, neutrophil activation results in fungal killing via differential mechanisms depending on the fungus, opsonization, and fungal morphogenic state (33–35).

Specifically, opsonized *Candida* killing depends on the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (described below), Syk, protein kinase C (PKC), and FcγR. Unopsonized *Candida* killing depends on Syk, CARD9, CR3, and phosphoinositide 3-kinase (PI3K). *Aspergillus* conidial killing depends on CR3, PI3K, and lactoferrin-mediated iron depletion, whereas extracellular *Aspergillus* hyphal killing relies on antibody-mediated opsonization, FcγR, Syk, PKC, PI3K, and the NADPH oxidase. Notably, neutrophils sense the large fungal filament size and produce neutrophil extracellular traps (NETs) (36). Although calprotectin, a NET constituent, is indispensable for control of candidiasis and aspergillosis (37, 38), the precise role of NETs during fungal infection remains elusive because of a lack of NET-specific molecules.

Although neutrophils are essential for protection during candidiasis and aspergillosis, a subset of infected neutropenic patients develops paradoxical clinical worsening during neutrophil recovery, inferring neutrophil-mediated immunopathology. Indeed, CCR1, the endoribonuclease MCPIP1, and the tyrosine kinase TEC contribute to neutrophil-induced immunopathology in fungus-infected mice and may be therapeutic targets for selected patients (39–41).

Monocytes, monocyte-derived DCs, and resident macrophages. Mononuclear phagocytes critically contribute to antifungal innate immunity (**Figure 2**). CCR2-dependent recruitment of mouse Ly6C^{hi} monocytes is indispensable for control of *Aspergillus*, *Cryptococcus*, *Histoplasma*, and *Blastomyces* in the lung, and *Candida* in the kidney and central nervous system (CNS) (42–44). CCR6-dependent protective DC recruitment also occurs during neutropenic aspergillosis (45). Monocytes and monocyte-derived DCs enable fungal control via inflammatory mediators (TNF-α, nitric oxide), fungal uptake and killing, and priming of neutrophil fungal killing and instruct protective adaptive immunity (described below). In fact, *Blastomyces* evades monocyte recruitment and ROS production by elaborating an aminopeptidase that cleaves CCR2-targeted chemokines and granulocyte-macrophage colony-stimulating factor (GM-CSF) (46).

Tissue-resident macrophages are first responders during fungal invasion. CX3CR1 is crucial for kidney-resident macrophage accumulation and survival, early macrophage-*Candida* interactions and fungal killing in tissue, and mouse survival during invasive candidiasis by inhibiting caspase-3-dependent apoptosis. In agreement, the dysfunctional allele *CX3CR1-M280* is an independent risk factor for candidemia and worse infection outcome in patients (47). Macrophages employ zinc sequestration–based nutritional immunity to control *Histoplasma*. Specifically, GM-CSF promotes STAT3- and STAT5-dependent zinc phagosomal sequestration via inducing zinc-metallothionein binding. The resultant increase in phagosomal H^+ mediates oxidative fungal clearance (48). β-glucan exposure and removal of cell wall melanin during *Aspergillus* uptake within macrophages activates LC3-associated phagocytosis, an Atg5-dependent autophagy pathway, and promotes fungal killing (49). Nonetheless, the broader implications of autophagy-mediated fungal killing remain unclear, with fungus-specific contrasting reports.

Trained immunity. Monocytes and macrophages promote lymphocyte-independent protection during systemic fungal rechallenge via epigenetic reprogramming that causes histone trimethylation and acetylation and results in trained immunity, an innate immunological memory with implications for fungal vaccine development. Specifically, β-glucans induce trained immunity in mouse and human monocytes via a Dectin-1/RAF-1/AKT/mTOR/HIF-1α pathway, associated with switching glucose metabolism from oxidative phosphorylation to aerobic glycolysis (50).

Other Innate Cells

Several other cells contribute to innate antifungal immunity. Plasmacytoid DCs, primarily known for antiviral immunity, promote Dectin-2-mediated protection during aspergillosis via

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cytokine release and fungal cytotoxicity, but they are detrimental during paracoccidioidomycosis via indoleamine 2,3-dioxygenase–dependent modulation of regulatory T cells (Tregs) (51, 52). Eosinophils are beneficial or detrimental depending on the model; they protect during acute aspergillosis but contribute to allergic responses associated with fungal sensitization (53).

Several innate lymphoid cell subsets mediate antifungal immune responses. Natural killer (NK) cells secrete GM-CSF, which primes neutrophil antifungal activity during invasive candidiasis (54). This axis requires Syk-dependent IL-23 production by DCs and type I interferon–dependent IL-15 production by Ly6C^{hi} monocytes for NK cell activation (25, 55). NKp30-mediated, PI3K/ERK-dependent perforin production exerts NK cell anticryptococcal activity. This axis is impaired in AIDS patients and is restored by IL-12 (56). CCL2-mediated NK cell recruitment enables protective IFN-γ production during neutropenic aspergillosis (57). Dectin-1- and MyD88-dependent β-glucan recognition by invariant NK T (iNKT) cells promotes CD1d$^+$ DC-primed innate responses against *Aspergillus*, *Candida*, and *Histoplasma*; it protects during aspergillosis but is detrimental during candidiasis and associated with IFN-γ-dependent immunopathology (58).

γδ T cells mediate IFN-γ-dependent anti-*Pneumocystis* protection (59) and IL-17-dependent protection during mucocutaneous candidiasis. Oral mucosal γδ T cells are major IL-17 producers together with αβ T cells and innate lymphoid cells-3, which collectively induce production of antimicrobial peptides (β-defensins) by epithelial cells that control mucosal *Candida* growth (60) (**Figure 3**). Dermal γδ T cells are the dominant cutaneous IL-17 source, primed by nociceptive sensory fibers that drive IL-23 production by CD301b$^+$ dermal DCs via calcitonin gene-related neuropeptide (60, 61). Ocular Vγ4$^+$ γδ T cell production of IL-17 depends on CD1d-mediated presentation of antigens of the ocular commensal *Corynebacterium mastitidis* by CD11b$^+$ DCs and protects during *Candida* (and *Pseudomonas*) topical infection (62).

Epithelial and endothelial cells are key innate responders during fungal invasion. E- and N-cadherin-dependent epithelial cell interaction with *Candida* agglutinin-like sequence-3 (Als3) protein and integrin $\alpha_5\beta_1$-dependent epithelial cell interaction with the *Aspergillus* thaumatin-like protein CalA promote fungal internalization and innate recognition (63, 64). During mucosal candidiasis, the cytolytic toxin candidalysin promotes epithelial cell c-FOS activation to produce IL-1α, IL-6, G-CSF, and GM-CSF (65). During oral candidiasis and pulmonary aspergillosis, epithelial cells regulate IL-1 receptor–dependent neutrophil influx (32, 66). During mucormycosis, a devastating infection preferentially affecting patients with diabetic ketoacidosis, the endothelial cell receptor glucose-regulated protein 78 (GRP78) promotes *Rhizopus* binding and endothelial cell invasion via fungal coat protein homolog 3 (CotH3) (67). Hyperglycemia, ketone bodies, and acidosis induce endothelial GRP78 and *Rhizopus* CotH3 expression, enabling fungal tissue invasion. Thus, CotH3-GRP78 underlie the selective susceptibility of diabetic patients to mucormycosis and are potential therapeutic targets.

ADAPTIVE IMMUNITY AGAINST FUNGI: PATHWAYS TO PROTECTION

When innate immunity fails, control of fungal invasion requires the development of an adaptive immune response consisting of antigen-specific T cells and antibodies (68). Importantly, the nature of the adaptive immune response is informed by the PRRs (particularly on DCs) mediating innate fungal recognition, the downstream signaling transduction pathways triggered, and the cytokine/chemokine responses stimulated. As discussed elsewhere in this review, CLRs play an outsized role in fungal recognition, and many studies have demonstrated that mutations or deletions in CLRs, or downstream molecules such as CARD9, lead to enhanced susceptibility to fungal infections.

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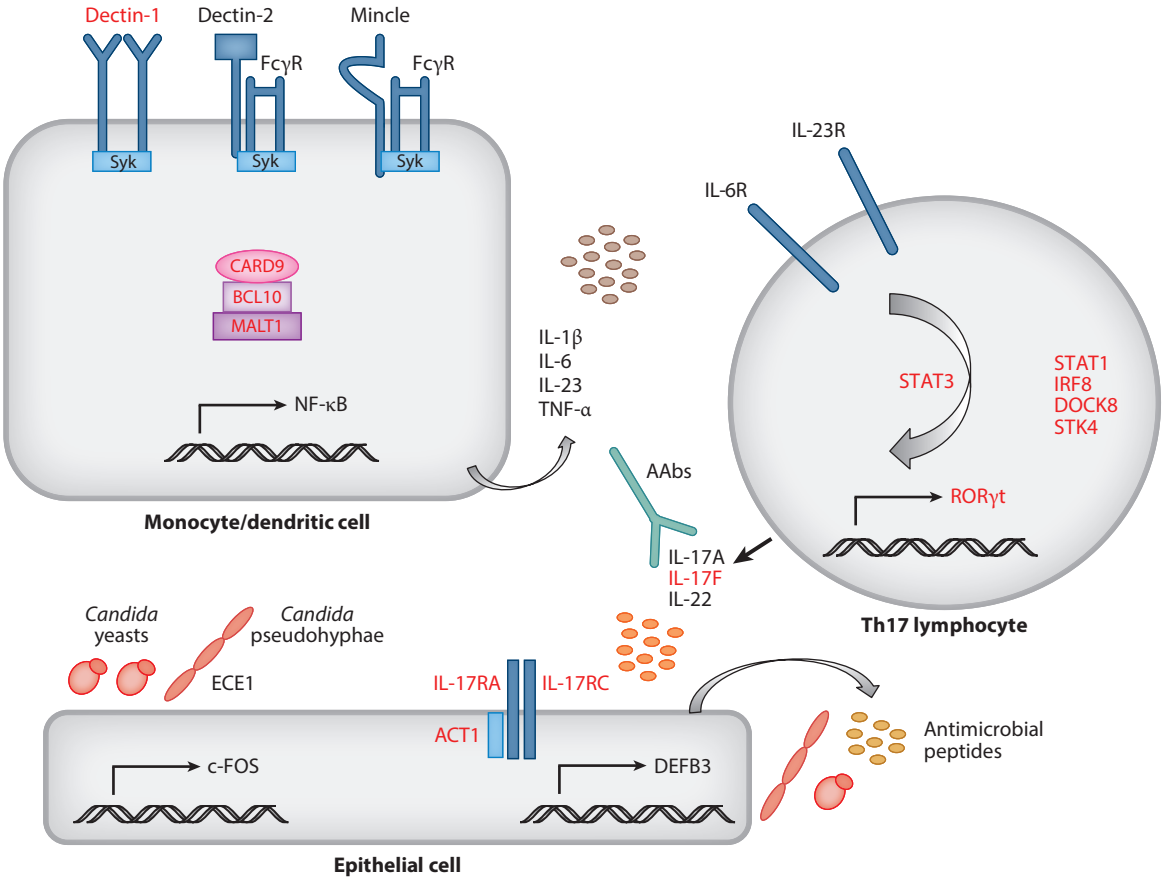

Figure 3

Mechanisms of antifungal host defense at the mucosal interface. *Candida* recognition by C-type lectin receptors leads to activation of the CARD9/BCL-10/MALT1 signaling complex, which promotes the production of proinflammatory cytokines that direct T cell differentiation toward the Th17 program. RORγt-mediated Th17 differentiation depends on STAT3 and is impaired in patients with Job's syndrome. CARD9, DOCK8, STK4, and IRF8 also contribute to Th17 differentiation, and monogenic disorders affecting each of these genes in humans result in CMC. CMC also develops in patients with *RORC* mutations that prevent T cell differentiation into the Th17 lineage. Gain-of-function *STAT1* mutations lead to STAT1 hyperphosphorylation, which generates a cytokine microenvironment that inhibits the differentiation of Th17 cells. Th17 cells produce IL-17 and IL-22. IL-17A and IL-17F, via their binding to IL-17RA and IL-17RC receptors and the downstream adaptor protein ACT1, induce the generation of potent antifungal antimicrobial peptides (β-defensins) by epithelial cells, which directly kill *Candida* at the mucosal surface. IL-17 is also produced by γδ T cells and group 3 innate lymphoid cells, in cell-specific frequencies that are mucosa specific. CMC is seen in patients with mutations in *IL17F*, *IL17RA*, *IL17RC*, and *ACT1*, which impair IL-17-dependent signaling, and in patients with AIRE deficiency (autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy) and thymoma who have neutralizing autoantibodies against IL-17 and IL-22. The cytolytic toxin candidalysin (encoded by Ece1) promotes epithelial cell c-FOS activation to produce IL-1α, IL-6, G-CSF, and GM-CSF after *Candida* infection. The *Candida* protein Als3 is an important adhesin and invasin via E- and N-cadherin binding on epithelial cells. In humans, inherited mutations in the genes in red font have been described to result in CMC. Abbreviations: AAbs, autoantibodies; AIRE, autoimmune regulator; Als3, agglutinin-like sequence 3; BCL-10, B cell lymphoma/leukemia 10; CARD9, caspase recruitment domain-containing protein 9; CMC, chronic mucocutaneous candidiasis; DOCK8, dedicator of cytokinesis 8; Ece1, extent of cell elongation protein 1; G-CSF; granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IRF8, interferon regulatory factor 8; MALT1, mucosa-associated lymphoid tissue lymphoma translocation protein 1; RORγt; RAR-related orphan receptor γ; STAT, signal transducer and activator of transcription; STK4, serine/threonine-protein kinase 4. Modified with permission from Reference 90.

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Antigen-Specific T Cell Responses

Although CD4$^+$ T cells can have direct activity against fungi, they mediate adaptive responses mainly via release of cytokines and by providing help to B cells and CD8$^+$ T cells. Loss of these functions contributes to the extraordinary susceptibility of AIDS patients to fungal infections. Studies in mice and in humans have demonstrated that DC recognition of whole fungi and fungal cell wall products, particularly β-1,3-D-glucan, leads to T cell responses that are Th1 and Th17 biased (69, 70). Clinical data, discussed below, suggest that Th1 (through production of IFN-γ) and Th17 (through production of IL-17) responses are critical for systemic and mucosal antifungal defenses, respectively. Th2 cells, by dampening Th1 responses and inducing alternatively activated macrophages, generally exacerbate infection and promote allergic inflammation, although they appear to be protective against *Pneumocystis* (71). Moreover, although T cells are necessary for resolution of infection, the inflammatory responses they generate can be deleterious owing to damage to host tissue (72). Tregs help fine-tune the immune response to limit collateral damage but can contribute to fungal persistence (73). In humans, Tregs are dispensable for antifungal host defense, as mutations in *FOXP3* (forkhead box P3) lead to absent Tregs and immunodysregulation, polyendocrinopathy, enteropathy X-linked (IPEX) syndrome, which causes multisystem autoimmunity but no fungal infection susceptibility (74).

The heterogeneity and plasticity of Th subsets have been increasingly recognized. For example, under defined conditions, Th17 cells can be induced to produce IFN-γ, IL-4, and IL-10, cytokines that are typically associated with Th1, Th2, and Treg cells, respectively (70, 75). In addition, stimulation of Th17 cells with IL-6 induces IL-22 production, which contributes to antifungal resistance at mucosal surfaces by controlling fungal growth and promoting epithelial integrity (76). Indeed, polyfunctional T cells have been described for all T cell subsets and the specific cytokines produced affect outcome following infection and vaccination.

While a preeminent role for CD4$^+$ T cells in host defenses against mycoses is firmly established, the contribution of CD8$^+$ T cells is less established, in part because inherited or acquired deficiencies that are exclusive to the CD8$^+$ T cell lineage without accompanying impairment in CD4$^+$ T cells and/or other cell subsets have not been described in humans thus far. For example, although patients with inherited ZAP70 deficiency, which results in absent CD8$^+$ T cells, are at risk for mucosal candidiasis and PJP, the fungal susceptibility cannot be cleanly attributed to CD8$^+$ T cell deficiency, as it coexists with combined immunodeficiency due to dysfunctional CD4$^+$ T cells (77). In agreement, although mice lacking CD8$^+$ T cells are more susceptible to challenge with some fungal pathogens, the phenotype observed is generally less severe than that seen with CD4$^+$ T cell depletion. Akin to CD4$^+$ T cells, subsets of CD8$^+$ T cells defined based on their expression of transcription factors and cytokine secretion have been described. The Tc1 and Tc17 subsets appear most relevant to host defenses against the mycoses, particularly in situations where CD4$^+$ T cells are depleted (78).

Antigen-Specific Antibody Responses

Multiple mechanisms have been described to explain how antibodies may protect the host against fungal infections (68, 79). Antibodies promote opsonophagocytosis directly via FcRs and indirectly through classical complement pathway activation with subsequent phagocytosis via complement receptors. However, fungi are resistant to complement-mediated lysis. Antibodies also modulate T cell responses and augment NK cell–mediated antifungal activity (80). Fungistatic and fungicidal effects of antibodies directed at fungal cell wall components, including melanin, HSP90, and β-1,3-D-glucan, have been reported (81, 82). *Cryptococcus* capsule–binding antibodies have direct effects on gene expression profiles, fungal metabolism, antifungal susceptibility, and biofilm formation

(82). Remarkably, an anticapsular antibody was recently shown to have hydrolytic activity against oligosaccharide and peptide substrates (83). Antibodies may also neutralize fungi, as with IgA and *Candida*, or fungal virulence factors, such as secreted proteases (84).

Antibodies reactive with fungal antigens can be protective, neutral, or disease enhancing (79). This may help explain why it has been difficult to convincingly demonstrate a role for antibodies in protection against naturally acquired infection (68). Interestingly, humans have natural antibodies, predominantly of the IgM isotype, reactive with fungal cell wall glycans, including β-1,3-D-glucan and chitin. Natural antibodies participate in innate defenses against fungi and help shape the adaptive immune response (85). In humans, antibody deficiency in X-linked agammaglobulinemia caused by mutations in Bruton's tyrosine kinase (*BTK*) does not typically result in mycoses, with the exception of a few reported cases of PJP (86).

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INHERITED FUNGAL SUSCEPTIBILITY: CRITICAL PATHWAYS AND IMMUNOTHERAPY LESSONS

The broader implementation of sequencing alongside careful phenotyping of patients with susceptibility to mucocutaneous and/or systemic mycoses has uncovered inborn errors of fungus-associated immune genes and pathways that have enhanced our understanding of molecular cues that mediate human antifungal host defense.

Mucocutaneous Antifungal Immunity Disorders

The delineation of the Th17 differentiation T cell program and the discovery that kindreds with loss-of-function mutations in *IL17F*, the two IL-17 receptor subunits (*IL17RA/IL17RC*), or the IL-17 receptor signaling adaptor *ACT1* develop chronic mucocutaneous candidiasis (CMC) without systemic fungal disease substantiated evidence from murine models that IL-17 signaling is critical for mucosal antifungal immunity (87–90) (**Figure 3**). Notably, *IL17F* and *IL17RC* mutations specifically cause CMC, whereas *IL17RA* or *ACT1* mutations also cause cutaneous staphylococcal and/or pulmonary bacterial infections, suggesting that IL-17E signaling may be important for bacterial immunity in the skin and lungs via mechanisms that remain to be elucidated (87–89).

Several other gene mutations result in CMC, typically combined with other infectious or non-infectious manifestations (90) (**Table 2**); IL-17 immune impairment has been implicated in most of them. For example, Job's syndrome caused by loss-of-function *STAT3* mutations impairs RORγt-dependent Th17 cell development (91), as do the recently described *RORC* mutations (92). Th17 development and/or differentiation is also compromised in patients with *DOCK8*, *IRF8*, *IL12RB1*, *CARD9*, or autosomal-dominant *STAT1* gain-of-function (GOF) mutations; the latter mutations account for ~50% of all patients with inherited CMC and cause STAT1 hyperphosphorylation, which induces IFN-α/β, IFN-γ, and IL-27. These cytokines in turn collectively inhibit Th17 generation via impaired SOCS3 expression and upregulation of the checkpoint inhibitor molecule PD-L1 (90, 93–95). Indeed, pharmacological JAK/STAT inhibition in these patients restores IL-17 immunity and results in CMC remission (96). Autoimmune regulator (AIRE) deficiency causes autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy (APECED), the only CMC-associated monogenic disorder in which CMC is the sole infection (97); neutralizing autoantibodies against Th17-cytokines are associated with CMC in AIRE-deficient patients, and in patients with thymoma (98). Other CMC-associated inherited disorders include severe combined immunodeficiency disorder (SCID); athymic DiGeorge syndrome, caused by 22q11.2 deletion; trisomy 21; and mutations in *MALT1*, *BCL10*, *STK4*, *IKBA*, *IL21R*, *CLEC7A*, and NEMO (NF-κB essential modulator) (90) (**Table 2**).

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Table 2 Immunological and clinical features of inborn errors of immunity that result in mucosal and systemic fungal infection susceptibility

Gene (mode of inheritance)	Clinical syndrome	Fungal infections	Other infectious and noninfectious manifestations	Immunological defects accounting for fungal susceptibility
CYBB (X linked), *CYBA*, *NCF1*, *NCF2*, *NCF4* (AR)	CGD	Aspergillosis Candidiasis	Infections by *Staphylococcus*, *Serratia*, *Nocardia*, *Burkholderia*; inflammatory bowel disease	Lack of superoxide generation
MPO (AR)		Candidiasis	None	Lack of hypochlorous acid
CTSC (AR)	Papillon-Lefèvre	Mucormycosis	Bacterial infections, periodontitis, palmoplantar keratoderma	Impaired activation of granule serine proteases
ELA2, *HAX1* (AR)	Severe congenital neutropenia	Aspergillosis, candidiasis	Periodontitis	Decreased neutrophil numbers
IFNGR1 (AD)	MSMD	Histoplasmosis, coccidioidomycosis	Intracellular bacterial and NTM infections	Impaired IFN-γ cellular responses
IL12RB1 (AR or AD)	MSMD	CMC, histoplasmosis, coccidioidomycosis, paracoccidioidomycosis, cryptococcosis	Intracellular bacterial and NTM infections	Impaired IL-12Rβ1–mediated Th17 differentiation (CMC), impaired IL-12/IL-23–mediated IFN-γ production (systemic infections)
IL17RA (AR)		CMC	Staphylococcal skin infections, lung bacterial infections, atopic dermatitis	Absent IL-17 cellular responses
IL17RC (AR)		CMC	Staphylococcal skin infections	Absent IL-17 cellular responses
IL17F (AD)		CMC	Asthma	Impaired IL-17F-dependent responses
ACT1 (AR)		CMC	Staphylococcal skin infections, atopic dermatitis	Absent IL-17 cellular responses
RORC (AR)		CMC	Mycobacterial infections	Impaired Th17 differentiation, abolished IL-17 production

(*Continued*)

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Table 2 (*Continued*)

Gene (mode of inheritance)	Clinical syndrome	Fungal infections	Other infectious and noninfectious manifestations	Immunological defects accounting for fungal susceptibility
IL2RG (X linked), *IL7RA*, *ADA*, *RAG1*, *RAG2*, *JAK3*, *ZAP70*, *ARTEMIS* (AR)	SCID	CMC, PJP	Bacterial and viral infections, graft-versus-host disease	Severe lymphopenia
STAT3 (AD)	HIES (Job's syndrome)	CMC, dermatophytosis, PJP, aspergillosis, cryptococcosis, histoplasmosis, coccidioidomycosis	Bacterial skin and lung infections, eczema, aneurysms, skeletal abnormalities	Impaired Th17 differentiation, impaired production of antimicrobial peptides
STAT1 (AD)		CMC, histoplasmosis, coccidioidomycosis, aspergillosis, fusariosis (skin)	Bacterial and viral infections, aneurysms, thyroid disease, autoimmunity, carcinomas	Enhanced cellular responses to IFN-α/β, IFN-γ, and IL-27, leading to inhibition of Th17 differentiation
GATA2 (AD)	MonoMAC syndrome	Aspergillosis, histoplasmosis, blastomycosis, cryptococcosis	NTM and HPV infections, hematological malignancies, lymphedema	Monocytopenia, decreased dendritic cells, neutrophil granule abnormalities
AIRE (AR or AD)	APECED	CMC	Multiorgan autoimmunity, ectodermal dysplasia	Neutralizing autoantibodies to Th17 cytokines
IRF8 (AR)		CMC	NTM infections	Decreased Th17 cells
CARD9 (AR)		CMC, *Candida* CNS infection, deep dermatophytosis, phaeohyphomycosis, extrapulmonary aspergillosis	None	Decreased Th17 cells, impaired neutrophil recruitment to the CNS, impaired fungal killing by neutrophils
MALT1 (AR)		CMC	Viral and bacterial infections, bronchiectasis, skin staphylococcal infections, hypogammaglobulinemia	Impaired T cell activation
BCL10 (AR)		CMC	Viral and NTM infections, diarrhea, hypogammaglobulinemia	Lymphopenia
CLEC7A (AR)		Vaginal candidiasis, dermatophytosis	None	Decreased IL-17 production by PBMCs

(*Continued*)

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Table 2 (*Continued*)

Gene (mode of inheritance)	Clinical syndrome	Fungal infections	Other infectious and noninfectious manifestations	Immunological defects accounting for fungal susceptibility
DOCK8 (AR)	HIES	CMC, dermatophytosis	Viral skin infections, malignancies, eczema	Impaired Th17 differentiation
TYK2 (AR)	HIES, MSMD	CMC	Bacterial, NTM, and viral infections; atopic dermatitis	Unknown
NEMO/IKBKG (X linked)	EDA-ID, HIGM	CMC, PJP	Bacterial, NTM, and viral infections; anhidrotic ectodermal dysplasia	Severe lymphopenia
IKBA (AD)	EDA-ID, HIGM	CMC, PJP	Bacterial and NTM infections, anhidrotic ectodermal dysplasia, inflammatory bowel disease	Severe lymphopenia, decreased proportion of Th17 cells
CD40L (X linked)	HIGM	PJP	Bacterial, parasitic, and NTM infections; inflammatory bowel disease	Impaired T cell responses
STK4 (AR)		CMC	Bacterial and viral infections, lymphoproliferation, heart abnormalities	Impaired T cell survival and proliferation
IL21R (AR)		PJP, CMC	Cholangitis and liver fibrosis associated with cryptosporidial infection	Impaired T cell activation
BTK	XLA	PJP	Bacterial infections	Impaired B cell signaling

Abbreviations: AD, autosomal dominant; APECED, autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy; AR, autosomal recessive; CGD, chronic granulomatous disease; CMC, chronic mucocutaneous candidiasis; CNS, central nervous system; EDA-ID, anhidrotic ectodermal dysplasia with immune deficiency; HIES, hyper-IgE syndrome; HIGM, hyper-IgM syndrome; HPV, human papilloma virus; MSMD, Mendelian susceptibility to mycobacterial disease; NTM, nontuberculous mycobacterial; PBMC, peripheral blood mononuclear cell; PJP, *Pneumocystis jirovecii* pneumonia; SCID, severe combined immunodeficiency disorder; XLA, X-linked agammaglobulinemia.

Systemic Antifungal Immunity Disorders

An array of inborn errors of immunity that affect the oxidative cytotoxic machinery, as well as fungal recognition and intracellular signaling pathways, predispose to a variety of systemic infections by inhaled molds, yeasts, and/or endemic dimorphic fungi.

Oxidative cytotoxicity disorders. Mutations in the NADPH oxidase subunits cause chronic granulomatous disease (CGD), which results in invasive mold and, less often, *Candida* infections through impaired superoxide generation and defective oxygen-dependent microbicidal phagocyte activity (**Figure 2**). Briefly, assembly of membrane-bound gp91phox and p22phox with the cytosolic p47phox-p67phox complex, p40phox, and RAC2 and their fusion with serine protease-containing granules on the phagolysosome form the NADPH oxidase complex; conversion of NADPH to $NADP^+$ generates superoxide that dismutates to hydrogen peroxide followed by myeloperoxidase-mediated hypochlorous and hypoiodous acid production, which are toxic for fungi and catalase-positive bacteria (90). Indeed, NADPH-mediated neutrophil killing induces an apoptosis-like programmed cell death pathway in *Aspergillus*. The expression level of the fungal antiapoptotic molecule BIR1, a homolog of human SURVIVIN, regulates susceptibility to host-induced programmed cell death induction (99). Importantly, the degree of residual phagocyte ROS production critically determines overall survival in CGD patients and varies depending on the disease-causing mutation (100). Gene therapy reconstitutes phagocyte oxidative cytotoxicity and fungal killing and controls fungal infection in CGD (101). IFN-γ decreases infection frequency and severity in CGD patients (102) and is the only FDA-approved immunotherapy-based treatment for mycoses; although IFN-γ boosts residual phagocyte ROS production in some patients, the mechanisms of IFN-γ protection remain elusive (100).

Although the oxidative burst protects against molds and *Candida* during ubiquitous lifetime exposures, ~60% and ~95% of CGD patients never develop aspergillosis and candidiasis, respectively (90). Moreover, complete myeloperoxidase deficiency causes absent hypochlorous acid but does not predispose to aspergillosis and only infrequently causes candidiasis (~5%) (90). In addition, patients with Papillon-Lefèvre syndrome due to cathepsin-C (*CTSC*) mutations, who exhibit impaired oxidative burst–dependent activation of granule serine proteases, only rarely develop mold infections (103). These observations collectively (*a*) underscore the fungus-specific dependence on different aspects of the intracellular oxidative cytotoxic machinery for protection and (*b*) indicate that nonoxidative effector phagocytic mechanisms can counterbalance absent oxidative cytotoxicity in most humans. In fact, the molecular cues that promote phagocyte nonoxidative fungal killing are poorly characterized, with CXCR1 and the endoplasmic reticulum protein JAGN1 recently identified (7, 104, 105).

Fungal recognition cascade disorders. Mendelian disorders have shed light on the relative contributions of different PRR pathways in human antifungal immunity. For example, although TLR gene polymorphisms modulate fungal infection susceptibility in intensive care unit patients (106), patients with *MYD88* mutations, the adaptor molecule downstream of TLRs, develop spontaneous bacterial, not fungal, disease (107). Similarly, although patients with inherited C5 deficiency and those receiving the anti-C5 antibody eculizumab infrequently develop mucosal and systemic mycoses, their susceptibility primarily maps to disseminated encapsulated bacterial infections (108).

Instead, patients with loss-of-function mutations of *CARD9*, coding for the adaptor molecule downstream of CLRs, exhibit fungus-specific infection susceptibility without predisposition to bacterial or viral disease. CARD9 deficiency displays distinctive characteristics among monogenic disorders of fungal susceptibility. First, it is the only known genetic disorder to cause both mucosal

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candidiasis and systemic candidiasis, which otherwise cleanly segregate with regard to differential requirements of immune responses for effective host defense.

Second, CARD9 deficiency strikingly leads to fungal infections with specific CNS predilection, thus exhibiting tissue tropism not typically seen with fungi in CARD9-sufficient individuals (109, 110). CARD9-deficient patients develop CNS candidiasis and extrapulmonary aspergillosis, in contrast to hepatosplenic candidiasis or pulmonary aspergillosis in patients with iatrogenic immunosuppression. Other mycoses in CARD9 deficiency include phaeohyphomycosis and deep-seated dermatophytosis, which may target the CNS (111, 112). This CNS tropism in CARD9 deficiency appears to relate, at least partly, to fungus-specific and CNS-specific impairment in neutrophil recruitment during infection, caused by defective neutrophil-targeted chemoattractant production by resident glial and recruited myeloid cells, whereas CARD9-deficient neutrophils do not exhibit cell-intrinsic chemotaxis defects (113). Defective fungal killing by the suboptimal neutrophils that reach the infected CNS may also contribute (114). In *Aspergillus*-infected lungs, which are spared by infection in CARD9-deficient humans, mononuclear phagocyte–mediated IL-1α and epithelial cell–mediated Myd88 signaling compensate for absent CARD9 and promote protective neutrophil recruitment (30). Therefore, CARD9 mediates tissue-, cell type–, and fungus-specific neutrophil recruitment during invasive fungal infection.

GM-CSF improved the outcome of a few CARD9-deficient patients with CNS candidiasis, presumably by bypassing the impaired H-RAS/RASGRF1/ERK-mediated GM-CSF response (115). Yet, not all CARD9-deficient infected patients respond to GM-CSF, and GM-CSF-treated *Card9*$^{-/-}$ mice are not rescued from fungal infection (Lionakis, unpublished observations). Hence, future mouse and human studies in patients with different *CARD9* mutations (i.e., nonsense versus missense mutations, mutations located in the CARD or coiled-coil domains of CARD9) should determine whether this or other immunotherapy approaches may circumvent the phagocyte recruitment and activation defects of CARD9 deficiency.

Signaling disorders. Mutations in the IL-12/IFN-γ signaling cascade highlight the importance of IL-12/IFN-γ-mediated lymphocyte/macrophage cross-talk in clearing intracellular fungal (and bacterial) pathogens, including *Histoplasma*, *Coccidioides*, *Paracoccidioides*, and *Cryptococcus*. Briefly, activated macrophages secrete IL-12, which stimulates NK and T cells to produce IFN-γ, which acts on macrophage IFN-γ receptors to activate STAT1, which upregulates the transcription of IFN-γ-related genes following nuclear translocation (90) (**Figure 4**). Some of these gene defects respond to IFN-γ or IFN-α immunotherapy. Consistent with these Mendelian disorders, adult-onset acquired immunodeficiency presenting with similar mycoses develops in patients with neutralizing IFN-γ autoantibodies (116). Adult-onset acquired immunodeficiency presenting with cryptococcosis, predominantly by *C. gattii*, develops in patients with neutralizing GM-CSF autoantibodies (117); these immunodeficiencies may be amenable to anti-CD20-targeted therapy that depletes B cells. Notably, these autoantibodies are enriched in patients of Asian ancestry who were born in Asia but not in those of Asian ancestry who were born elsewhere, implicating host genetic and environmental coinfluence. Similarly, disseminated coccidioidomycosis is enriched among African Americans, people of Asian ancestry, and pregnant women, and chronic paracoccidioidomycosis exhibits a male predominance, indicating that host genetic and hormonal factors influence the phenotypic expression of endemic mycoses (118, 119). Besides CMC, patients with *STAT1* GOF mutations and Job's syndrome develop invasive mycoses with differing features; intracellular dimorphic fungi cause disseminated infections in *STAT1* GOF mutations and infections with an unusual intestinal tropism in Job's syndrome. Furthermore, molds cause pulmonary infections in the absence of structural lung disease in *STAT1* GOF mutations, while mold

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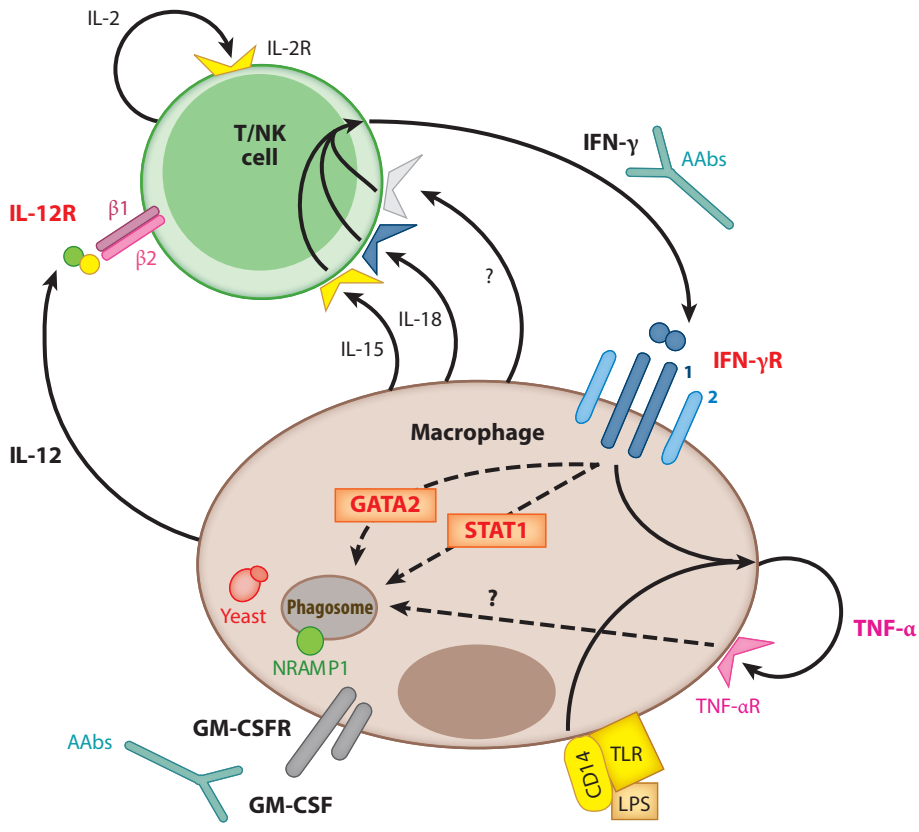

Figure 4

Molecular cues that underlie protective lymphocyte-macrophage cross talk during infection by intracellular fungi. The interaction between monocytes/macrophages and T/NK cells is critical for control of facultative intracellular fungi (endemic dimorphic fungi, *Cryptococcus*). IL-12 is released by monocytes/macrophages in response to fungal uptake and binds to the IL-12 receptor (which consists of β1 and β2 subunits) on T and NK cells. IL-12/IL-12 receptor engagement activates STAT4 via TYK2 and JAK2 and results in the release of IFN-γ. IFN-γ binds to the IFN-γ receptor (which consists of two subunits, IFN-γR1 and IFN-γR2) on monocytes/macrophages and via JAK1/JAK2 leads to STAT1 activation that enables recruitment of NRAMP1 to the phagosomal membrane and intracellular fungal killing. GATA2 is critical for monocyte, DC, and NK cell development and effector function, and autosomal-dominant *GATA2* mutations in humans result in intracellular fungal infection susceptibility. Mutations in IL-12 receptor subunit β1, in either subunit of the IFN-γ receptor, and gain-of-function *STAT1* mutations also lead to Mendelian susceptibility to intracellular fungi (and mycobacteria). TNF-α and GM-CSF bind to their cognate receptors on the surface of monocytes/macrophages, resulting in cell activation. Pharmacological inhibition of TNF-α (*pink font*) and neutralizing autoantibodies against GM-CSF or IFN-γ result in infection susceptibility by intracellular fungi. Inherited mutations in genes encoding the proteins in red font have been described to result in infections by intracellular fungi in humans. The molecular mechanisms by which GATA2, STAT1, and TNF-α promote intracellular fungal killing remain poorly understood (*dashed lines*). Abbreviations: AAbs, autoantibodies; DC, dendritic cell; GATA2, GATA binding protein 2; GM-CSF, granulocyte-macrophage colony-stimulating factor; JAK, Janus kinase; NK, natural killer; NRAMP1, natural resistance–associated macrophage protein 1; STAT, signal transducer and activator of transcription; TYK2, tyrosine kinase 2.

infections develop following structural lung disease secondary to recurrent bacterial pneumonias in Job's syndrome (90).

Haploinsufficiency in the transcription factor GATA2 causes myelodysplasia, lymphedema, and broad-spectrum infection susceptibility including aspergillosis, histoplasmosis, and cryptococcosis (90). Decreased/absent monocytes and DCs are seen, which may contribute to infection susceptibility. CD40 and its downstream NEMO, the regulatory subunit of the IKK complex that activates NF-κB, STAT3, and IL-21 receptor signaling underlie the protective $CD4^+$ T cell/macrophage cross-talk against PJP, which develops in patients with SCID, Job's syndrome, and mutations in NEMO, *CD40L*, *IL21R*, or *IKBA* (90, 107).

ACQUIRED IMMUNODEFICIENCIES THAT PREDISPOSE TO MYCOSES

The AIDS pandemic and significant advances in transplantation and immunomodulatory therapeutic strategies for malignant and autoimmune conditions have markedly increased the number of patients with acquired innate and/or adaptive immune defects that manifest with mucosal and/or systemic mycoses.

AIDS

In the 1980s and 1990s, before the combination antiretroviral therapy (ART) era, opportunistic (including fungal) infections were a leading cause of mortality in AIDS patients; infection-related mortality has now declined in the developed world but remains a critical problem in developing countries with limited access to ART; indeed, cryptococcosis causes ~200,000 deaths per year globally (120).

The natural history of mycoses in AIDS patients highlights (*a*) the importance of $CD4^+$ T cells in immunity against certain fungi, and (*b*) the different threshold of $CD4^+$ T cell decline associated with fungus-specific infection susceptibility. Before ART, >90% of AIDS patients with $CD4^+$ T cell counts $<200/mm^3$ developed mucosal candidiasis. Mice expressing the HIV transgene, which recapitulate several aspects of human HIV infection pathogenesis, are susceptible to oral candidiasis due to defective T cell production of IL-17 and IL-22 (121, 122). Interestingly, AIDS heightens the risk for oral and esophageal, not vulvovaginal, candidiasis. Conversely, antibiotic-treated healthy individuals develop vulvovaginal, not oral or esophageal, candidiasis (122). These observations highlight the mucosa-specific dependence on microbiome factors for *Candida* control; *Lactobacillus*, the predominant genus in the human vaginal microbiota, may contribute to vaginal anti-*Candida* immunity via tryptophan catabolite generation, which mediates aryl hydrocarbon receptor–dependent IL-22 production (123).

Concerning systemic mycoses, without ART and antifungal prophylaxis, 70–80% of AIDS patients with $CD4^+$ T cell counts $<200/mm^3$ develop PJP, 5–8% with $CD4^+$ T cell counts $<100/mm^3$ develop cryptococcal meningoencephalitis, and ~5% residing in endemic areas develop disseminated histoplasmosis and coccidioidomycosis when $CD4^+$ T cells decline below $150/mm^3$ and $250/mm^3$, respectively. Instead, AIDS patients rarely develop aspergillosis, typically when other risk factors like glucocorticoid treatment exist.

AIDS patients with cryptococcosis display *Cryptococcus*-specific $CD4^+$ T cell responses characterized by IFN-γ and TNF-α production; importantly, IFN-γ– and TNF-α–predominant T cell responses are associated with improved survival (124). In agreement, enrichment of IFN-γ, TNF-α, and other proinflammatory cytokines in the *Cryptococcus*-infected cerebrospinal fluid is associated with better prognosis (125, 126). Consistent with these data and the protective Th1

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immunity in *Cryptococcus*-infected mice, adjunct IFN-γ immunotherapy in AIDS patients leads to faster fungal clearance from the cerebrospinal fluid, a well-established surrogate of survival (127).

Although critical for fungal control, $CD4^+$ T cells also exert detrimental effects. Immune reconstitution inflammatory syndrome (IRIS) is a paradoxical worsening of infections, predominantly cryptococcosis and PJP (and mycobacterial infections), despite control of HIV viremia and microbiological control of the infection and is seen in up to 30% of AIDS patients upon ART initiation and $CD4^+$ T cell reconstitution (128). The risk of IRIS is greater with severe $CD4^+$ T cell lymphopenia, higher HIV viremia, and active infection at ART initiation. Patients with AIDS-IRIS exhibit enriched effector memory, PD-1^+, Ki-67^+, HLA-DR^+, Th1/Th17-biased $CD4^+$ T cells, which express more ICOS and CTLA-4 compared to patients without IRIS; elevated serum IFN-γ and IL-7 are seen (128). In mouse IRIS models associated with *Cryptococcus* and PJP (and mycobacteria), $CD4^+$ T cells are sufficient to drive immunopathology (129). As with AIDS-IRIS patients, induction of IL-6, IFN-γ, and TNF-α is seen in mouse tissues; however, although IFN-γ (and IL-6) is a major mediator of pathology in mycobacteria-driven IRIS, it was insufficient to promote cryptococcal IRIS, indicating that other signals are involved, either alone or combined with IFN-γ (129, 130).

Transplantation

Allogeneic hematopoietic stem cell transplantation (HSCT) and solid organ transplantation revolutionized the prognosis of malignant diseases and end-organ failure, respectively. However, successful engraftment of donor cells and organs requires iatrogenic immunosuppression in transplant recipients, which predisposes to life-threatening opportunistic (including fungal) infections.

The major risk factor for fungal disease immediately following allogeneic HSCT is neutropenia (131). Already in the 1960s, it was recognized that the risk of life-threatening infections in cancer patients correlates with the depth and duration of neutropenia, with neutrophil counts $<100/mm^3$ for prolonged periods conferring greatest susceptibility (132). Up to 15–20% of HSCT recipients develop invasive candidiasis and mold infections (primarily aspergillosis) during the preengraftment neutropenic period without antifungal prophylaxis (131). Gastrointestinal mucosal disruption by the transplant conditioning chemotherapy, and antibiotic-induced dysbiosis that impairs *Candida* colonization resistance due to suppressed HIF-1α and LL-37 further contribute to candidiasis; indeed, mucosal injury, antibiotics, and neutropenia synergistically enhance mouse susceptibility (133, 134). In fact, preclinical evaluation of nongenotoxic conditioning during HSCT that utilizes an internalizing immunotoxin targeting the hematopoietic cell–restricted CD45 receptor shows promise for minimizing toxicity during HSCT. Indeed, this method avoids neutropenia, preserves thymic and bone marrow niches, and restores antifungal immunity relative to conventional irradiation-based conditioning (135).

For over 50 years, transfusions of high-dose G-CSF/dexamethasone-mobilized granulocytes have been employed to combat infections in neutropenic patients, with variable results. These transfusions may improve the outcome of certain patients with profound and prolonged neutropenia and refractory mold infections; however, their preparation and delivery are associated with significant logistical and technical difficulties that limit widespread use (136). Antifungal drug–loaded granulocyte transfusions have also been investigated, with promising preclinical results (137). Studies have also examined whether shortening the neutropenic period with colony-stimulating factors improves patient outcomes. GM-CSF, not G-CSF, decreased fungal infection incidence and improved survival after allogeneic HSCT (138). In mice, M-CSF, not G-CSF, instructed myeloid commitment in hematopoietic stem cells via inducing the myeloid transcription factor PU.1, enhanced production of myeloid donor cells, and improved survival after *Aspergillus*

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(and *Pseudomonas*) infection (139). Hence, M-CSF and GM-CSF show promise for further human studies.

After neutrophil recovery, some HSCT recipients develop graft-versus-host disease (GVHD), caused by donor-derived alloreactive T cells that attack recipient skin, liver, and gut. GVHD requires glucocorticoid-based immunosuppression to prevent end-organ damage and confers infection susceptibility. Glucocorticoids exert pleiotropic qualitative and quantitative immunosuppressive effects on myeloid and lymphoid cells via inhibiting NF-κB, AP-1, and other transcription factors. Briefly, glucocorticoids cause lymphopenia and monocytopenia; impair lymphocyte proliferation, activation, and migration; inhibit NK cell cytotoxicity; and suppress endothelial adherence, phagocytosis, degranulation, oxidative burst, and trafficking of neutrophils and monocytes/macrophages (140). Not surprisingly, glucocorticoids dose-dependently heighten the risk for aspergillosis, candidiasis, and PJP, whereas cryptococcosis and endemic mycoses are less common (131). In 10–50% of cases, steroid-refractory GVHD ensues, which necessitates prolonged higher glucocorticoid exposure combined with immunomodulators targeting the IL-2 receptor α chain in T cells (CD25) and/or CD52, which depletes T cells, and/or TNF-α, which further increases infection risk. GVHD immunosuppressive treatment also predisposes to cytomegalovirus reactivation, which appears to independently increase *Aspergillus* risk, as do respiratory viral infections via yet-unknown immune-modulating mechanisms (131, 141).

Notably, gene polymorphisms in HSCT donors and/or recipients confer risk for aspergillosis by affecting the function of recipient myeloid or donor epithelial cells, respectively. These include the PRR genes *CLEC7A*, *TLR4*, *TLR6*, and *PTX3* (pentraxin 3, which mediates phagocyte fungal uptake and killing) and the Th1-immunity molecules *CXCL10*, *IFNG*, and *TNFR1* (142–144). Collectively, these findings show promise for devising precision-medicine risk stratification and prognostication strategies for HSCT.

Solid organ transplantation also predisposes to mycoses, mostly owing to immunosuppressants administered to prevent organ rejection. Invasive candidiasis and aspergillosis are most common, but cryptococcosis and endemic mycoses also develop, more often than they do after HSCT (145). Fungal infection risk varies depending on the transplanted organ, with small intestine recipients carrying the greatest risk, followed by lung, liver, heart, pancreas, and kidney recipients. Different organs confer fungus-specific infection risk, with candidiasis being most common in abdominal organ transplantation, related to *Candida* gut colonization and surgical-site infections, whereas mold infections are most common following lung transplantation, reflecting airborne exposure. Glucocorticoids and immunomodulators targeting CD52, CD25, and/or TNF-α synergistically increase infection risk following solid organ transplantation, whereas calcineurin inhibitors exert differential fungus-specific immunomodulatory effects (145–147).

Biologic Agents and Small-Molecule Kinase Inhibitors

The advent of mechanism-based biologic agents and small-molecule kinase inhibitors has revolutionized the treatment of inflammatory and malignant diseases; although they are less immunosuppressive than glucocorticoids and nonselective chemotherapeutic drugs, the use of these agents has underscored the importance of specific molecules and pathways in pathogen (including fungal) immunity (**Table 3**).

Cytokine targets. Patients with rheumatoid arthritis and inflammatory bowel disease receiving TNF-α inhibitors develop fungal (and mycobacterial) infections (148). Disseminated endemic mycoses, related to impaired IFN-γ production and granuloma formation induced by TNF-α blockade, are most common (149). Infectious risk is greater with anti-TNF-α antibodies

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Table 3 Biologic agents and small-molecule kinase inhibitors associated with human fungal infection susceptibility

Biologic agent/kinase inhibitor	Structure	Target	FDA-approved clinical indications	Fungal infection susceptibility	Immunological defects accounting for fungal susceptibility
Infliximab	Mouse-human chimeric IgG1k mAb	TNF-α	RA, JIA, PsA, AS, IBD, psoriasis	Histoplasmosis, coccidioidomycosis, aspergillosis, systemic candidiasis	Impaired granuloma formation and suppressed IFN-γ production (endemic fungi), impaired phagocyte recruitment and effector function (*Aspergillus*, *Candida*)
Adalimumab	Humanized IgG1k mAb				
Etanercept	Two p75 TNF-α soluble receptors fused to the Fc portion of IgG1				
Certolizumab pegol	Recombinant Fab′ antibody fragment against TNF-α conjugated to a polyethylene glycol				
Golimumab	Humanized IgG1k mAb				
Brodalumab	Humanized IgG2 mAb	IL-17RA	Psoriasis	Mucosal candidiasis	Impaired IL-17 cellular responses
Secukinumab	Humanized IgG1k mAb	IL-17A	Psoriasis	Mucosal candidiasis	Impaired IL-17 cellular responses
Ixekizumab	Humanized IgG4 mAb	IL-17A	Psoriasis	Mucosal candidiasis	Impaired IL-17 cellular responses
Risankizumab	Humanized IgG1k mAb	IL-23p19	IBD	Mucosal candidiasis	Impaired IL-17 cellular responses
Ustekinumab	Humanized IgG1k mAb	IL-12p40	Psoriasis, PsA, IBD	Mucosal candidiasis	Impaired IL-17 cellular responses
Tocilizumab	Humanized IgG1k mAb	IL-6R	RA, JIA, giant cell arteritis	Systemic candidiasis, cryptococcosis, PJP	Impaired phagocyte recruitment and activation (*Candida*)
Alemtuzumab	Humanized IgG1k mAb	CD52	CLL, MS	PJP, cryptococcosis	Severe T cell lymphopenia
Rituximab	Mouse-human chimeric IgG1k mAb	CD20	CLL, NHL, RA, Wegener granulomatosis, microscopic polyangiitis	PJP	Severe B cell lymphopenia, impaired anti-*Pneumocystis* $CD4^+$ T cell responses
Ruxolitinib	Kinase inhibitor	JAK1/2	Myelofibrosis	Cryptococcosis, PJP, penicilliosis	Impaired lymphocyte differentiation and activation, impaired monocyte/macrophage activation, downregulation of cytokine production (IL-2, IL-4, IL-7, IL-9, IL-15, IL-21)
Tofacitinib	Kinase inhibitor	JAK1/3	RA		

(*Continued*)

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Table 3 (*Continued*)

Biologic agent/kinase inhibitor	Structure	Target	FDA-approved clinical indications	Fungal infection susceptibility	Immunological defects accounting for fungal susceptibility
Ibrutinib	Kinase inhibitor	BTK	CLL, mantle cell lymphoma, Waldenstroöm macroglobulinemia	Aspergillosis, PJP, cryptococcosis, mucormycosis, fusariosis	Impaired macrophage activation
Idelalisib	Kinase inhibitor	p110δ (PI3K)	Relapsed CLL and NHL	PJP	Impaired lymphocyte activation
Dasatinib	Kinase inhibitor	BCR/ABL	CML	PJP	Impaired lymphocyte activation
Abatacept	Chimeric CTLA4 and IgG1 Fc fusion protein	CTLA-4	RA, JIA	PJP	Impaired CD28 costimulation and T cell activation
Natalizumab	Humanized IgG4k mAb	α_4-integrin	MS	Cryptococcosis	Lymphocyte recruitment
Sorafenib	Dual kinase inhibitor	C-RAF; B-RAF	Renal cell cancer, hepatocellular cancer	Mucosal candidiasis, cutaneous *Rhodotorula* infection	Unknown
Bevacizumab	Humanized IgG1 mAb	VEGF	Colorectal cancer, cervical cancer, lung cancer, glioblastoma	Aspergillosis, fusariosis	Unknown

Abbreviations: AS, ankylosing spondylitis; BCR, breakpoint cluster region; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; IBD, inflammatory bowel disease; JIA, juvenile idiopathic arthritis; mAb, monoclonal antibody; MS, multiple sclerosis; NHL, non-Hodgkin lymphoma; PJP, *Pneumocystis jirovecii* pneumonia; PsA, psoriatic arthritis; RA, rheumatoid arthritis.

(infliximab/adalimumab) relative to soluble TNF-α receptor (etanercept) (148). This higher risk relates to (*a*) inhibition of both soluble and cell-associated TNF-α and (*b*) induction of complement-mediated lysis of TNF-α-expressing cells, which is not observed with etanercept, which targets only soluble TNF-α (150).

Psoriasis patients receiving IL-17/IL-23 signaling blockade therapies develop mucosal, not systemic, candidiasis, consistent with the significance of IL-17 signaling in antifungal mucosal immunity. The frequency of candidiasis ranges between 2% and 5%, depending on the biologic agent: Brodalumab, targeting IL-17RA, and risankizumab, targeting IL-23, confer the greatest risk, followed by secukinumab/ixekizumab (IL-17A) and ustekinumab (IL-12p40) (151–153).

The IL-6 receptor–targeting tocilizumab is occasionally associated with systemic candidiasis, consistent with impaired neutrophil recruitment and increased *Candida* susceptibility of *Il6*$^{-/-}$ mice (154, 155). Less often, cryptococcosis or PJP occurs. Instead, the IL-1 receptor–targeting anakinra does not increase fungal susceptibility, consistent with absence of fungal disease in patients with inherited *MYD88* mutations who have impaired IL-1R signaling (154).

Cell-surface and intracellular signaling targets. Prolonged and profound T cell and B cell depletion develops with antibodies that target cell surface CD52 (alemtuzumab) and CD20 (rituximab), respectively. Not unexpectedly, alemtuzumab predisposes to the AIDS-defining infections PJP and cryptococcosis (156). Rituximab promotes PJP susceptibility; beyond B cell depletion, the predisposition maps to impaired anti-*Pneumocystis* CD4^{+} T cell responses (157, 158).

The JAK inhibitors ruxolitinib and tofacitinib impair JAK/STAT signaling, suppress lymphocyte differentiation and function, inhibit monocyte/macrophage activation, and downregulate cytokine production (159); thus, infections occur in ruxolitinib/tofacitinib-treated patients, including cryptococcosis, PJP, and penicilliosis (154). The BTK inhibitor ibrutinib impairs B cell receptor signaling and TLR9-BTK-calcineurin-NFAT activation in macrophages and causes aspergillosis, cryptococcosis, and PJP (86, 160). Emerging reports of mycoses in patients treated with other targeted molecules warrant further surveillance and investigation. These include (*a*) PJP with the PI3K inhibitor idelalisib, the BCR (breakpoint cluster region)/ABL tyrosine kinase inhibitor dasatinib, and the CTLA4 modulator abatacept, which blocks CD28-dependent costimulation and T cell activation; (*b*) cryptococcal meningitis with the anti–α_4 integrin antibody natalizumab, which blocks CNS lymphocyte recruitment in multiple sclerosis; (*c*) mucocutaneous *Candida* and *Rhodotorula* infections with the C-RAF/B-RAF tyrosine kinase inhibitor sorafenib; and (*d*) mold infections with the anti-VEGF antibody bevacizumab, which inhibits angiogenesis (154, 161–164).

While the aforementioned agents enhance fungal susceptibility, targeting other pathways may improve infection outcomes. For example, blockade of the checkpoint inhibitor PD-1/PD-L1 pathway in mice protects against candidiasis and histoplasmosis (165, 166), and adjunct treatment with the anti-PD-1 antibody nivolumab and IFN-γ was effective in a patient with mucormycosis (167); thus, the role of PD-1/PD-L1 modulation in managing human mycoses merits further investigation.

FUNGAL VACCINES AND ANTIBODY THERAPY

Despite the substantial morbidity and mortality associated with fungal diseases, there are no licensed vaccines to protect humans against fungal infections. Some fungal diseases, including coccidioidomycosis, histoplasmosis, and vulvovaginal candidiasis, affect relatively immunocompetent individuals frequently enough to make vaccines targeting persons at risk for these diseases feasible. However, most patients with invasive mycoses are severely immunocompromised and

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therefore might not mount a strong immune response after vaccination (168, 169). Maximal efficacy may require vaccination prior to anticipated immunosuppression, for example, in persons on transplant waiting lists or HIV-infected individuals with relatively high $CD4^+$ T cell counts. An alternative strategy is to design vaccines to elicit protective responses in an arm of the immune system that is (relatively) not immunocompromised (168).

Panfungal vaccines seek to exploit common antigens present on medically important fungi. Such vaccines are attractive because they have the potential to protect against a broad range of fungal diseases. As discussed above, most fungal cell walls contain β-1,3-D-glucans. However, following fungal infection, the antibody response to this glycan is quite poor. A vaccine consisting of the β-1,3-D-glucan, laminarin, conjugated to diphtheria toxoid elicits strong antibody responses in mice and protects the animals against challenge with species of *Candida*, *Aspergillus*, and *Cryptococcus* (81). Other vaccines that protect against multiple genera of fungi have been described, including heat-killed *Saccharomyces* yeast, which affords protection by a mechanism that is antibody independent (170); and the protein calnexin, which elicits T cell–mediated protection against many of the medically important members of the fungal phylum Ascomycota, including the major endemic mycoses and *Aspergillus* (171). Another antigen that elicits cross-kingdom protection, albeit one that is more species specific, is recombinant *Candida albicans* Als3 (172). rAls3 has structural homology with two *Staphylococcus aureus* surface proteins. A vaccine containing rAls3 with an alum adjuvant protects mice against *Candida* and *Staphylococcus* and is undergoing clinical trials in humans with recurrent vulvovaginal candidiasis.

Protection against many virulent wild-type fungi has been demonstrated following vaccination of mice with live, attenuated stains. In an approach that has implications for vaccinating HIV-infected patients, vaccine-mediated protection against blastomycosis was retained even when $CD4^+$ T cells were depleted because of the emergence of protective IL-17-producing $CD8^+$ T cells (173). Similarly, a vaccine strain of *Cryptococcus* genetically modified to express IFN-γ protected $CD4^+$ T cell–deficient mice against experimental cryptococcosis (174). Other promising live, attenuated vaccine strategies involve pulmonary administration of deletion mutants of *Coccidioides* and *Cryptococcus* (175, 176). There are caveats to the use of live vaccines; they must be sufficiently attenuated so as not to cause disease in immunocompromised persons, and inflammatory reactions at the vaccination site can be limiting (168). Moreover, there are theoretical concerns about inducing autoimmunity given that humans and fungi are eukaryotic, with many shared homologous proteins. Protective responses have also been observed following administration of vaccines consisting of killed whole organisms (176, 177). In a double-blind, phase 3 clinical trial, 2,867 individuals were randomized to receive either placebo or a vaccine composed of formaldehyde-killed *Coccidioides* spherules (177). While there was a reduction, albeit statistically insignificant, in the number of cases in the vaccine group, tolerability of the vaccine was poor, owing to local and systemic inflammatory reactions.

The aforementioned issues with live and killed whole organism vaccines have prompted studies on subunit vaccines. Numerous fungal antigens have been described that elicit protective responses in vaccine models of mycoses (178, 179). In addition to identification of candidate antigens, development of subunit vaccines requires formulating the antigens with adjuvants or into a delivery system. The adaptive immune response to vaccine antigens is informed by the innate immune sensors stimulated by the vaccine (168). Alum, the adjuvant used in most licensed vaccines, elicits mostly antibody responses. Antigen-specific T cell responses, when seen, tend to be Th2 biased. A major challenge in vaccinology is to develop adjuvants that stimulate stronger T cell responses; it has been particularly difficult to elicit protective $CD8^+$ T cell responses without using live vaccines (168, 178). Moreover, vaccines designed to elicit T cell–mediated protection must take into

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account the diversity of the human MHC proteins responsible for presentation of antigen-derived peptides to T cells.

Innate recognition of β-1,3-D-glucans, mannans, and chitosan on fungi can lead to robust adaptive immune responses to associated fungal proteins. This fundamental finding has been exploited in vaccine development by using these glycans as adjuvants and delivery systems for both fungal and nonfungal antigens (180). Mice immunized with β-glucan particles containing trapped antigens develop strong and long-lasting Th1- and Th17-biased T cell and humoral responses (181, 182). β-glucan particles are recognized by Dectin-1; however, mice lacking this receptor still develop antigen-specific responses to trapped antigens inside the particles owing to complement activation and subsequent phagocytosis via complement receptors (69). Mice vaccinated with cryptococcal alkaline extracts embedded in β-glucan particles are partially protected following challenge with *C. neoformans* and *C. gattii* (183). Immunotherapeutic vaccines consisting of killed *Saccharomyces* expressing tumor or viral antigens have been tested in phase 1 and 2 clinical studies; $CD4^+$ and $CD8^+$ T cell responses to the heterologous antigens were observed (184).

While both mammalian and fungal cells glycosylate proteins, the patterns of *N*- and *O*-linked glycosylation differ (185). Fungal glycoproteins generally feature extensive mannosylation with exposed mannose groups, whereas mammalian mannosylation is less extensive and rarely terminal. Mannose receptors, including DC-SIGN, Dectin-2, Mincle, and Langerin (CD207), can recognize free and surface-exposed fungal mannoproteins (180, 186, 187). Importantly, DC uptake, processing, and presentation are more efficient when antigen is mannosylated, suggesting that immunogenicity can be increased if antigen mannosylation is incorporated into vaccine design (180, 188–190). Moreover, combining ligands for mannose receptors and TLRs results in synergistic immune responses (191, 192). The adjuvant properties of chitin and chitosan have also been studied; for both polymers, their immunological properties vary depending upon source, size, and method of preparation (193, 194).

Passive Antibody and T Cell Therapy

As noted above, immunocompromised patients generally are unable to mount protective responses following vaccination. Therefore, researchers have studied the efficacy of passive administration of antibodies and T cells to prevent and treat mycotic infections. In models of systemic candidiasis, cryptococcosis, histoplasmosis, and aspergillosis, mice receiving monoclonal antibodies against surface-exposed epitopes were at least partially protected from a subsequent lethal infection (169). A trial of a monoclonal anticapsular antibody in humans with cryptococcal meningitis failed to show clinical benefit, but there was a transient drop in titers of capsular polysaccharide in the blood (195). A promising target for antibody therapy is poly-*N*-acetylglucosamine (PNAG), a conserved antigen exposed on many prokaryotic and eukaryotic pathogens, including the fungi *Candida*, *Aspergillus*, and *Cryptococcus* (196). Antibodies to deacetylated glycoforms of PNAG protected mice from experimental *Candida* keratitis.

Although the development of autoantibodies can be limiting, humans are universal recipients of passively administered antibodies. In contrast, adoptive transfer of T cells is limited by HLA type. Nevertheless, promising feasibility studies have been performed, spurred in part by advances in techniques to expand and genetically engineer antigen-specific T cells. In a mouse model of aspergillosis in the setting of allogeneic HSCT, survival of mice was prolonged following adoptive transfer of *Aspergillus*-specific $CD4^+$ T cells (197). In a pilot study in humans with aspergillosis following haploidentical hematopoietic transplantation, *Aspergillus*-specific donor-derived $CD4^+$ Th1 clones were expanded and adoptively transferred into 10 patients (198). The infection resolved in 9 of the patients, compared with only 6 of 13 control patients. T cell expansion

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was slow; more rapid methods to expand fungus-specific human peripheral blood T cells based on expression of the activation markers CD154 and CD137 show promise but await human testing (199). Finally, adoptive transfer of T cells genetically modified to express chimeric antigen receptors (CARs) specific for tumor antigens is undergoing promising clinical trials in cancer patients. This approach was adapted to treat mycotic infections by modifying T cells to express Dectin-1, resulting in antifungal CAR T cells with specificity for β-1,3-D-glucan (200). Adoptive transfer of the bioengineered cells protected mice in two distinct models of aspergillosis but has yet to be tried in humans.

CONCLUSIONS

In this review, we highlight recent immunological discoveries ranging from basic studies in mouse models of fungal disease to studies of human cohorts with inherited and acquired susceptibility to mycoses. The dramatic expansion of immunosuppressed patients who develop life-threatening mycoses in recent decades has been accompanied by significant advances in our knowledge concerning the cellular and molecular immune factors that protect humans from lifetime ubiquitous fungal exposures. The challenge moving forward will be to continue to translate our improved understanding of the innate and adaptive mechanisms that are deployed by the host to combat fungal invasion to the development of novel strategies for risk assessment, immunotherapy, prognostication, and vaccination of patients with fungal infections.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

We apologize to our many colleagues whose valuable contributions we were not able to cite because of space constraints. This work was supported by the Division of Intramural Research, NIAID, NIH (M.S.L.) and NIH grants AI025780, AI102618, and HL112671 from NIAID and NHLBI (S.M.L.).

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